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PATENT

Docket No.: 176/60792 (6-11415-868)

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Mahin D. Maines )  
Serial No. : 09/606,129 ) Examiner:  
Cnfrm. No. : 5529 ) D. Ramirez  
Filed : June 28, 2000 ) Art Unit:  
For : BILIVERDIN REDUCTASE FRAGMENTS ) 1652  
AND VARIANTS, AND METHODS OF USING )  
BILIVERDIN REDUCTASE AND SUCH )  
FRAGMENTS AND VARIANTS )

## STATEMENTS IN ACCORDANCE WITH 37 C.F.R. § 1.821

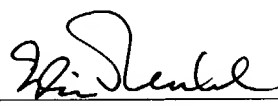
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Sir:

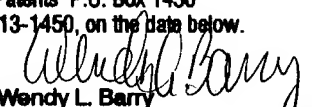
In accordance with 37 C.F.R. § 1.821, applicant hereby submits a Sequence Listing (21 pages) on paper and on a computer readable 3.5" Diskette. In accordance with 37 C.F.R. § 1.821(f), applicant submits that the contents of the paper copy and the computer readable form are the same. In accordance with 37 C.F.R. § 1.821(g), applicant submits that the Sequence Listing contains no new matter.

Respectfully submitted,

Dated: March 3, 2004

  
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| Date<br><u>3/3/04</u>  | <br>Wendy L. Barry |



## SEQUENCE LISTING

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MAR 12 2004

&lt;110&gt; Maino, Mahin D.

<120> BILIVERDIN REDUCTASE FRAGMENTS AND VARIANTS, AND  
METHODS OF USING BILIVERDIN REDUCTASE AND SUCH  
FRAGMENTS AND VARIANTS

&lt;130&gt; 176/60792

&lt;140&gt; 09/606,129

&lt;141&gt; 2000-06-28

&lt;150&gt; 60/141,309

&lt;151&gt; 1999-06-28

&lt;150&gt; 60/163,223

&lt;151&gt; 1999-11-03

&lt;160&gt; 37

&lt;170&gt; PatentIn Ver. 2.1

&lt;210&gt; 1

&lt;211&gt; 296

&lt;212&gt; PRT

&lt;213&gt; Homo sapiens

&lt;400&gt; 1

Met Asn Ala Glu Pro Glu Arg Lys Phe Gly Val Val Val Val Gly Val  
1 5 10 15

Gly Arg Ala Gly Ser Val Arg Met Arg Asp Leu Arg Asn Pro His Pro  
20 25 30

Ser Ser Ala Phe Leu Asn Leu Ile Gly Phe Val Ser Arg Arg Glu Leu  
35 40 45

Gly Ser Ile Asp Gly Val Gln Gln Ile Ser Leu Glu Asp Ala Leu Ser  
50 55 60

Ser Gln Glu Val Glu Val Ala Tyr Ile Cys Ser Glu Ser Ser Ser His  
65 70 75 80

Glu Asp Tyr Ile Arg Gln Phe Leu Asn Ala Gly Lys His Val Leu Val  
85 90 95

Glu Tyr Pro Met Thr Leu Ser Leu Ala Ala Ala Gln Glu Leu Trp Glu

| 100   | 105 | 110 |
|---|-----|-----|
| Leu Ala Glu Gln Lys Gly Lys Val Leu His Glu Glu His Val Glu Leu |     |     |
| 115   | 120 | 125 |
| Leu Met Glu Glu Phe Ala Phe Leu Lys Lys Glu Val Val Gly Lys Asp |     |     |
| 130   | 135 | 140 |
| Leu Leu Lys Gly Ser Leu Leu Phe Thr Ser Asp Pro Leu Glu Glu Asp |     |     |
| 145   | 150 | 155 |
| Arg Phe Gly Phe Pro Ala Phe Ser Gly Ile Ser Arg Leu Thr Trp Leu |     |     |
| 165   | 170 | 175 |
| Val Ser Leu Phe Gly Glu Leu Ser Leu Val Ser Ala Thr Leu Glu Glu |     |     |
| 180   | 185 | 190 |
| Arg Lys Glu Asp Gln Tyr Met Lys Met Thr Val Cys Leu Glu Thr Glu |     |     |
| 195   | 200 | 205 |
| Lys Lys Ser Pro Leu Ser Trp Ile Glu Glu Lys Gly Pro Gly Leu Lys |     |     |
| 210   | 215 | 220 |
| Arg Asn Arg Tyr Leu Ser Phe His Phe Lys Ser Gly Ser Leu Glu Asn |     |     |
| 225   | 230 | 235 |
| Val Pro Asn Val Gly Val Asn Lys Asn Ile Phe Leu Lys Asp Gln Asn |     |     |
| 245   | 250 | 255 |
| Ile Phe Val Gln Lys Leu Leu Gly Gln Phe Ser Glu Lys Glu Leu Ala |     |     |
| 260   | 265 | 270 |
| Ala Glu Lys Lys Arg Ile Leu His Cys Leu Gly Leu Ala Glu Glu Ile |     |     |
| 275   | 280 | 285 |
| Gln Lys Tyr Cys Cys Ser Arg Lys                                 |     |     |
| 290   | 295 |     |

<210> 2

<211> 1070

<212> DNA

<213> Homo sapiens

<400> 2

ggggtggcgc ccggagctgc acggagagcg tgcccgtcag tgaccgaaga agagaccaag 60  
atgaatgcag agcccgagag gaagtttggc gtggtggtgg ttggtggtgg ccgagccggc 120  
tccgtgcgga tgagggactt gcggaatcca cacccttct cagcgcttct gaacctgatt 180

```

ggcttcgtgt cgagaagggg gctcgggagc attgatggag tccagcagat ttctttggag 240
gatgctcttt ccagccaaga ggtggaggtc gcctatatct gcagtgagag ctccagccat 300
gaggactaca tcaggcagtt ccttaatgct ggcaagcacg tccttgtgga ataccccatg 360
acactgtcat tggcgggcgc tcaggaactg tgggagctgg ctgagcagaa aggaaaagtc 420
ttgcacgagg agcatgttga actcttgatg gaggaattcg ctttcctgaa aaaagaagtg 480
gtggggaaaag acctgctgaa agggtcgctc ctcttcacat ctgaccggtt ggaagaagac 540
cggtttggct tccctgcatt cagcggcatc tctcgactga cctggctggt ctccctcttt 600
ggggagcttt ctcttgtgtc tgccactttg gaagagcgaa aggaagatca gtatatgaaa 660
atgacagtgt gtctggagac agagaagaaa agtccactgt catggattga agaaaaagga 720
cctggtctaa aacgaaacag atattttaagc ttccatttca agtctgggtc cttggagaat 780
gtgccaaatg taggagtga taagaacata tttctgaaag atcaaaatat atttgtccag 840
aaactcttgg gccagtcttc tgagaaggaa ctggctgctg aaaagaaacg catcctgcac 900
tgcttggggc ttgcagaaga aatccagaaa tattgctgtt caaggaagta agaggaggag 960
gtgatgtagc acttccaaga tggcaccagc atttggttct tctcaagagt tgaccattat 1020
ctctattctt aaaattaaac atgttgggga aacaaaaaaa aaaaaaaaaa 1070

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<210> 3

<211> 296

<212> PRT

<213> Homo sapiens

<400> 3

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Met Asn Thr Glu Pro Glu Arg Lys Phe Gly Val Val Val Val Gly Val
  1                      5                      10                      15

```

```

Gly Arg Ala Gly Ser Val Arg Met Arg Asp Leu Arg Asn Pro His Pro
          20                      25                      30

```

```

Ser Ser Ala Phe Leu Asn Leu Ile Gly Phe Val Ser Arg Arg Glu Leu
          35                      40                      45

```

```

Gly Ser Ile Asp Gly Val Gln Gln Ile Ser Leu Glu Asp Ala Leu Ser
          50                      55                      60

```

```

Ser Gln Glu Val Glu Val Ala Tyr Ile Cys Ser Glu Ser Ser Ser His
          65                      70                      75                      80

```

```

Glu Asp Tyr Ile Arg Gln Phe Leu Asn Ala Gly Lys His Val Leu Val
          85                      90                      95

```

```

Glu Tyr Pro Met Thr Leu Ser Leu Ala Ala Ala Gln Glu Leu Trp Glu
          100                      105                      110

```

```

Leu Ala Glu Gln Lys Gly Lys Val Leu His Glu Glu His Val Glu Leu
          115                      120                      125

```

```

Leu Met Glu Glu Phe Ala Phe Leu Lys Lys Glu Val Val Gly Lys Asp

```

|   |     |             |
|---|-----|-------------|
| 130   | 135 | 140         |
| Leu Leu Lys Gly Ser Leu Leu Phe Thr Ala Gly Pro Leu Glu Glu Glu |     |             |
| 145   | 150 | 155 160     |
| Arg Phe Gly Phe Pro Ala Phe Ser Gly Ile Ser Arg Leu Thr Trp Leu |     |             |
|   | 165 | 170 175     |
| Val Ser Leu Phe Gly Glu Leu Ser Leu Val Ser Ala Thr Leu Glu Glu |     |             |
|   | 180 | 185 190     |
| Arg Lys Glu Asp Gln Tyr Met Lys Met Thr Val Cys Leu Glu Thr Glu |     |             |
|   | 195 | 200 205     |
| Lys Lys Ser Pro Leu Ser Trp Ile Glu Glu Lys Gly Pro Gly Leu Lys |     |             |
|   | 210 | 215 220     |
| Arg Asn Arg Tyr Leu Ser Phe His Phe Lys Ser Gly Ser Leu Glu Asn |     |             |
|   | 225 | 230 235 240 |
| Val Pro Asn Val Gly Val Asn Lys Asn Ile Phe Leu Lys Asp Gln Asn |     |             |
|   | 245 | 250 255     |
| Ile Phe Val Gln Lys Leu Leu Gly Gln Phe Ser Glu Lys Glu Leu Ala |     |             |
|   | 260 | 265 270     |
| Ala Glu Lys Lys Arg Ile Leu His Cys Leu Gly Leu Ala Glu Glu Ile |     |             |
|   | 275 | 280 285     |
| Gln Lys Tyr Cys Cys Ser Arg Lys                                 |     |             |
|   | 290 | 295         |

<210> 4

<211> 295

<212> PRT

<213> Rattus norvegicus

<400> 4

|   |
|---|
| Met Asp Ala Glu Pro Lys Arg Lys Phe Gly Val Val Val Val Gly Val |
| 1 5 10 15   |
| Gly Arg Ala Gly Ser Val Arg Leu Arg Asp Leu Lys Asp Pro Arg Ser |
| 20 25 30  |
| Ala Ala Phe Leu Asn Leu Ile Gly Phe Val Ser Arg Arg Glu Leu Gly |
| 35 40 45  |

Ser Leu Asp Glu Val Arg Gln Ile Ser Leu Glu Asp Ala Leu Arg Ser  
 50 55 60

Gln Glu Ile Asp Val Ala Tyr Ile Cys Ser Glu Ser Ser Ser His Glu  
 65 70 75 80

Asp Tyr Ile Arg Gln Phe Leu Gln Ala Gly Lys His Val Leu Val Glu  
 85 90 95

Tyr Pro Met Thr Leu Ser Phe Ala Ala Ala Gln Glu Leu Trp Glu Leu  
 100 105 110

Ala Ala Gln Lys Gly Arg Val Leu His Glu Glu His Val Glu Leu Leu  
 115 120 125

Met Glu Glu Phe Glu Phe Leu Arg Arg Glu Val Leu Gly Lys Glu Leu  
 130 135 140

Leu Lys Gly Ser Leu Arg Phe Thr Ala Ser Pro Leu Glu Glu Glu Arg  
 145 150 155 160

Phe Gly Phe Pro Ala Phe Ser Gly Ile Ser Arg Leu Thr Trp Leu Val  
 165 170 175

Ser Leu Phe Gly Glu Leu Ser Leu Ile Ser Ala Thr Leu Glu Glu Arg  
 180 185 190

Lys Glu Asp Gln Tyr Met Lys Met Thr Val Gln Leu Glu Thr Gln Asn  
 195 200 205

Lys Gly Leu Leu Ser Trp Ile Glu Glu Lys Gly Pro Gly Leu Lys Arg  
 210 215 220

Asn Arg Tyr Val Asn Phe Gln Phe Thr Ser Gly Ser Leu Glu Glu Val  
 225 230 235 240

Pro Ser Val Gly Val Asn Lys Asn Ile Phe Leu Lys Asp Gln Asp Ile  
 245 250 255

Phe Val Gln Lys Leu Leu Asp Gln Val Ser Ala Glu Asp Leu Ala Ala  
 260 265 270

Glu Lys Lys Arg Ile Met His Cys Leu Gly Leu Ala Ser Asp Ile Gln  
 275 280 285

Lys Leu Cys His Gln Lys Lys  
 290 295

<210> 5  
 <211> 1081  
 <212> DNA  
 <213> Rattus norvegicus

<400> 5  
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 aacctctgtc tgtcttcgga cactgactga agagaccgag atggatgccg agccaaagag 120  
 gaaatttgga gtggtagtgg ttggtgttgg cagagctggc tcggtgaggc tgagggactt 180  
 gaaggatcca cgctctgcag cattcctgaa cctgattgga tttgtgtcca gacgagagct 240  
 tgggagcctt gatgaagtac ggcagatttc tttggaagat gctctccgaa gccaaagat 300  
 tgatgtcgcc tatatttgca gtgagagttc cagccatgaa gactatatac ggcagtttct 360  
 gcaggctggc aagcatgtcc tcgtggaata ccccatgaca ctgtcatttg cggcggccca 420  
 ggagctgtgg gagctggccg cacagaaagg gagagtcctg catgaggagc acgtggaact 480  
 cttgatggag gaattcgaat tcctgagaag agaagtgttg gggaaagagc tactgaaagg 540  
 gtctcttcgc ttcacagcta gccactgga agaagagaga tttggcttcc ctgcgttcag 600  
 cggcatttct cgcctgacct ggctggcttc cctcttcggg gagctttctc ttatttctgc 660  
 caccttgga gagcgaaaag aggatcagta tatgaaaatg accgtgcagc tggagaccca 720  
 gaacaagggc ctgctgtcat ggattgaaga gaaagggcct ggcttaaaaa gaaacagata 780  
 tgtaaacttc cagttcactt ctgggtccct ggaggaagtg ccaagtgtag gggtaataa 840  
 gaacattttc ctgaaagatc aggatataat tgttcagaag ctcttagacc aggtctctgc 900  
 agaggacctg gctgctgaga agaagcgcat catgcattgc ctggggctgg ccagcgacat 960  
 ccagaagctt tgccaccaga agaagtgaag aggaagcttc agagacttct gaagggggcc 1020  
 agggtttggc cctatcaacc attcaccttt agctcttaca attaaacatg tcagataaac 1080  
 a 1081

<210> 6  
 <211> 6  
 <212> PRT  
 <213> Artificial Sequence

<220>  
 <223> Description of Artificial Sequence: hydrophobic  
 domain of BVR

<220>  
 <221> PEPTIDE  
 <222> (2)  
 <223> where X is any aa

<400> 6  
 Phe Xaa Val Val Val Val  
 1 5

<210> 7

<211> 6  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: nucleotide  
binding domain of BVR

<220>  
<221> PEPTIDE  
<222> (2)  
<223> where X is any aa

<220>  
<221> PEPTIDE  
<222> (4) .. (5)  
<223> where X is any aa

<400> 7  
Gly Xaa Gly Xaa Xaa Gly  
1 5

<210> 8  
<211> 8  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence:  
oxidoreductase domain of BVR

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Ala Gly Lys His Val Leu Val Glu  
1 5

<210> 9  
<211> 29  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: leucine  
zipper of BVR

<220>  
<221> PEPTIDE



<222> (2)..(7)

<223> where X is any aa

<220>

<221> PEPTIDE

<222> (9)..(14)

<223> where X is any aa

<220>

<221> PEPTIDE

<222> (16)..(21)

<223> where X is any aa

<220>

<221> PEPTIDE

<222> (23)..(28)

<223> where X is any aa

<400> 9

Leu Xaa Xaa Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa Xaa Xaa Xaa Lys Xaa  
1 5 10 15

Xaa Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa Xaa Xaa Xaa Leu  
20 25

<210> 10

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: kinase motif  
of BVR

<400> 10

Ser Arg Arg

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<210> 11

<211> 3

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: kinase motif  
of BVR

<400> 11  
Lys Gly Ser  
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<210> 12  
<211> 3  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: kinase motif  
of BVR

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<221> PEPTIDE  
<222> (3)  
<223> where X is any aa

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Phe Gly Xaa  
1

<210> 13  
<211> 7  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: nuclear  
localization signal of BVR

<400> 13  
Gly Leu Lys Arg Asn Arg Tyr  
1 5

<210> 14  
<211> 5  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: methylation  
site of BVR

<400> 14

Pro Gly Leu Lys Arg

1 5

<210> 15

<211> 14

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: zinc finger  
domain of BVR

<220>

<221> PEPTIDE

<222> (3)..(12)

<223> where X is any aa

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His Cys Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Cys Cys

1 5 10

<210> 16

<211> 7

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: protein  
kinase C enhancing domain

<220>

<221> PEPTIDE

<222> (5)

<223> where X is any aa

<400> 16

Lys Lys Arg Ile Xaa His Cys

1 5

<210> 17

<211> 8

<212> PRT

<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: protein  
kinase C inhibiting domain

<220>  
<221> PEPTIDE  
<222> (3)  
<223> where X is any aa

<220>  
<221> PEPTIDE  
<222> (5)..(7)  
<223> where X is any aa

<400> 17  
Gln Lys Xaa Cys Xaa Xaa Xaa Lys  
1 5

<210> 18  
<211> 7  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: protein  
kinase C enhancer peptide of rBVR

<400> 18  
Lys Lys Arg Ile Met His Cys  
1 5

<210> 19  
<211> 8  
<212> PRT  
<213> Artificial Sequence

<220>  
<223> Description of Artificial Sequence: protein  
kinase C inhibitor peptide of rBVR

<400> 19  
Gln Lys Leu Cys His Gln Lys Lys  
1 5

<210> 20

<211> 1014  
 <212> PRT  
 <213> Homo sapiens

<400> 20

|     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |     |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Ala | Glu | Ser | Ser | Asp | Lys | Leu | Tyr | Arg | Val | Glu | Tyr | Ala | Lys | Ser | 1   | 5   | 10  | 15  |
| Gly | Arg | Ala | Ser | Cys | Lys | Lys | Cys | Ser | Glu | Ser | Ile | Pro | Lys | Asp | Ser | 20  | 25  | 30  |     |
| Leu | Arg | Met | Ala | Ile | Met | Val | Gln | Ser | Pro | Met | Phe | Asp | Gly | Lys | Val | 35  | 40  | 45  |     |
| Pro | His | Trp | Tyr | His | Phe | Ser | Cys | Phe | Trp | Lys | Val | Gly | His | Ser | Ile | 50  | 55  | 60  |     |
| Arg | His | Pro | Asp | Val | Glu | Val | Asp | Gly | Phe | Ser | Glu | Leu | Arg | Trp | Asp | 65  | 70  | 75  | 80  |
| Asp | Gln | Gln | Lys | Val | Lys | Lys | Thr | Ala | Glu | Ala | Gly | Gly | Val | Thr | Gly | 85  | 90  | 95  |     |
| Lys | Gly | Gln | Asp | Gly | Ile | Gly | Ser | Lys | Ala | Glu | Lys | Thr | Leu | Gly | Asp | 100 | 105 | 110 |     |
| Phe | Ala | Ala | Glu | Tyr | Ala | Lys | Ser | Asn | Arg | Ser | Thr | Cys | Lys | Gly | Cys | 115 | 120 | 125 |     |
| Met | Glu | Lys | Ile | Glu | Lys | Gly | Gln | Val | Arg | Leu | Ser | Lys | Lys | Met | Val | 130 | 135 | 140 |     |
| Asp | Pro | Glu | Lys | Pro | Gln | Leu | Gly | Met | Ile | Asp | Arg | Trp | Tyr | His | Pro | 145 | 150 | 155 | 160 |
| Gly | Cys | Phe | Val | Lys | Asn | Arg | Glu | Glu | Leu | Gly | Phe | Arg | Pro | Glu | Tyr | 165 | 170 | 175 |     |
| Ser | Ala | Ser | Gln | Leu | Lys | Gly | Phe | Ser | Leu | Leu | Ala | Thr | Glu | Asp | Lys | 180 | 185 | 190 |     |
| Glu | Ala | Leu | Lys | Lys | Gln | Leu | Pro | Gly | Val | Lys | Ser | Glu | Gly | Lys | Arg | 195 | 200 | 205 |     |
| Lys | Gly | Asp | Glu | Val | Asp | Gly | Val | Asp | Glu | Val | Ala | Lys | Lys | Lys | Ser | 210 | 215 | 220 |     |
| Lys | Lys | Glu | Lys | Asp | Lys | Asp | Ser | Lys | Leu | Glu | Lys | Ala | Leu | Lys | Ala |     |     |     |     |

|   |     |     |     |     |     |     |
|---|-----|-----|-----|-----|-----|-----|
| 225   |     | 230 |     | 235 |     | 240 |
| Gln Asn Asp Leu Ile Trp Asn Ile Lys Asp Glu Leu Lys Lys Val Cys |     |     |     |     |     |     |
|   | 245 |     | 250 |     | 255 |     |
| Ser Thr Asn Asp Leu Lys Glu Leu Leu Ile Phe Asn Lys Gln Gln Val |     |     |     |     |     |     |
|   | 260 |     | 265 |     | 270 |     |
| Pro Ser Gly Glu Ser Ala Ile Leu Asp Arg Val Ala Asp Gly Met Val |     |     |     |     |     |     |
|   | 275 |     | 280 |     | 285 |     |
| Phe Gly Ala Leu Leu Pro Cys Glu Glu Cys Ser Gly Gln Leu Val Phe |     |     |     |     |     |     |
|   | 290 |     | 295 |     | 300 |     |
| Lys Ser Asp Ala Tyr Tyr Cys Thr Gly Asp Val Thr Ala Trp Thr Lys |     |     |     |     |     |     |
| 305   |     | 310 |     | 315 |     | 320 |
| Cys Met Val Lys Thr Gln Thr Pro Asn Arg Lys Glu Trp Val Thr Pro |     |     |     |     |     |     |
|   | 325 |     | 330 |     | 335 |     |
| Lys Glu Phe Arg Glu Ile Ser Tyr Leu Lys Lys Leu Lys Val Lys Lys |     |     |     |     |     |     |
|   | 340 |     | 345 |     | 350 |     |
| Gln Asp Arg Ile Phe Pro Pro Glu Thr Ser Ala Ser Val Ala Ala Thr |     |     |     |     |     |     |
|   | 355 |     | 360 |     | 365 |     |
| Pro Pro Pro Ser Thr Ala Ser Ala Pro Ala Ala Val Asn Ser Ser Ala |     |     |     |     |     |     |
|   | 370 |     | 375 |     | 380 |     |
| Ser Ala Asp Lys Pro Leu Ser Asn Met Lys Ile Leu Thr Leu Gly Lys |     |     |     |     |     |     |
| 385   |     | 390 |     | 395 |     | 400 |
| Leu Ser Arg Asn Lys Asp Glu Val Lys Ala Met Ile Glu Lys Leu Gly |     |     |     |     |     |     |
|   | 405 |     | 410 |     | 415 |     |
| Gly Lys Leu Thr Gly Thr Ala Asn Lys Ala Ser Leu Cys Ile Ser Thr |     |     |     |     |     |     |
|   | 420 |     | 425 |     | 430 |     |
| Lys Lys Glu Val Glu Lys Met Asn Lys Lys Met Glu Glu Val Lys Glu |     |     |     |     |     |     |
|   | 435 |     | 440 |     | 445 |     |
| Ala Asn Ile Arg Val Val Ser Glu Asp Phe Leu Gln Asp Val Ser Ala |     |     |     |     |     |     |
|   | 450 |     | 455 |     | 460 |     |
| Ser Thr Lys Ser Leu Gln Glu Leu Phe Leu Ala His Ile Leu Ser Pro |     |     |     |     |     |     |
| 465   |     | 470 |     | 475 |     | 480 |
| Trp Gly Ala Glu Val Lys Ala Glu Pro Val Glu Val Val Ala Pro Arg |     |     |     |     |     |     |

| 485 |     |     |     |     |     |     |     |     |     | 490 |     |     |     |     | 495 |  |  |  |  |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|--|
| Gly | Lys | Ser | Gly | Ala | Ala | Leu | Ser | Lys | Lys | Ser | Lys | Gly | Gln | Val | Lys |  |  |  |  |
|     |     |     | 500 |     |     |     |     | 505 |     |     |     |     | 510 |     |     |  |  |  |  |
| Glu | Glu | Gly | Ile | Asn | Lys | Ser | Glu | Lys | Arg | Met | Lys | Leu | Thr | Leu | Lys |  |  |  |  |
|     |     | 515 |     |     |     |     | 520 |     |     |     |     | 525 |     |     |     |  |  |  |  |
| Gly | Gly | Ala | Ala | Val | Asp | Pro | Asp | Ser | Gly | Leu | Glu | His | Ser | Ala | His |  |  |  |  |
|     |     | 530 |     |     |     | 535 |     |     |     |     | 540 |     |     |     |     |  |  |  |  |
| Val | Leu | Glu | Lys | Gly | Gly | Lys | Val | Phe | Ser | Ala | Thr | Leu | Gly | Leu | Val |  |  |  |  |
| 545 |     |     |     |     | 550 |     |     |     | 555 |     |     |     |     |     | 560 |  |  |  |  |
| Asp | Ile | Val | Lys | Gly | Thr | Asn | Ser | Tyr | Tyr | Lys | Leu | Gln | Leu | Leu | Glu |  |  |  |  |
|     |     |     |     | 565 |     |     |     | 570 |     |     |     |     |     | 575 |     |  |  |  |  |
| Asp | Asp | Lys | Glu | Asn | Arg | Tyr | Trp | Ile | Phe | Arg | Ser | Trp | Gly | Arg | Val |  |  |  |  |
|     |     |     | 580 |     |     |     |     | 585 |     |     |     |     | 590 |     |     |  |  |  |  |
| Gly | Thr | Val | Ile | Gly | Ser | Asn | Lys | Leu | Glu | Gln | Met | Pro | Ser | Lys | Glu |  |  |  |  |
|     |     | 595 |     |     |     |     | 600 |     |     |     |     | 605 |     |     |     |  |  |  |  |
| Asp | Ala | Ile | Glu | His | Phe | Met | Lys | Leu | Tyr | Glu | Glu | Lys | Thr | Gly | Asn |  |  |  |  |
|     |     | 610 |     |     |     | 615 |     |     |     |     | 620 |     |     |     |     |  |  |  |  |
| Ala | Trp | His | Ser | Lys | Asn | Phe | Thr | Lys | Tyr | Pro | Lys | Lys | Phe | Tyr | Pro |  |  |  |  |
| 625 |     |     |     |     | 630 |     |     |     |     | 635 |     |     |     |     | 640 |  |  |  |  |
| Leu | Glu | Ile | Asp | Tyr | Gly | Gln | Asp | Glu | Glu | Ala | Val | Lys | Lys | Leu | Thr |  |  |  |  |
|     |     |     |     | 645 |     |     |     | 650 |     |     |     |     |     | 655 |     |  |  |  |  |
| Val | Asn | Pro | Gly | Thr | Lys | Ser | Lys | Leu | Pro | Lys | Pro | Val | Gln | Asp | Leu |  |  |  |  |
|     |     |     | 660 |     |     |     |     | 665 |     |     |     |     | 670 |     |     |  |  |  |  |
| Ile | Lys | Met | Ile | Phe | Asp | Val | Glu | Ser | Met | Lys | Lys | Ala | Met | Val | Glu |  |  |  |  |
|     |     | 675 |     |     |     |     | 680 |     |     |     |     | 685 |     |     |     |  |  |  |  |
| Tyr | Glu | Ile | Asp | Leu | Gln | Lys | Met | Pro | Leu | Gly | Lys | Leu | Ser | Lys | Arg |  |  |  |  |
|     |     | 690 |     |     |     | 695 |     |     |     |     | 700 |     |     |     |     |  |  |  |  |
| Gln | Ile | Gln | Ala | Ala | Tyr | Ser | Ile | Leu | Ser | Glu | Val | Gln | Gln | Ala | Val |  |  |  |  |
| 705 |     |     |     |     | 710 |     |     |     |     | 715 |     |     |     |     | 720 |  |  |  |  |
| Ser | Gln | Gly | Ser | Ser | Asp | Ser | Gln | Ile | Leu | Asp | Leu | Ser | Asn | Arg | Phe |  |  |  |  |
|     |     |     |     | 725 |     |     |     | 730 |     |     |     |     |     | 735 |     |  |  |  |  |
| Tyr | Thr | Leu | Ile | Pro | His | Asp | Phe | Gly | Met | Lys | Lys | Pro | Pro | Leu | Leu |  |  |  |  |

|   |     |     |
|---|-----|-----|
| 740   | 745 | 750 |
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| 755   | 760 | 765 |
| Leu Asp Ile Glu Val Ala Tyr Ser Leu Leu Arg Gly Gly Ser Asp Asp |     |     |
| 770   | 775 | 780 |
| Ser Ser Lys Asp Pro Ile Asp Val Asn Tyr Glu Lys Leu Lys Thr Asp |     |     |
| 785   | 790 | 795 |
| Ile Lys Val Val Asp Arg Asp Ser Glu Glu Ala Glu Ile Ile Arg Lys |     |     |
| 805   | 810 | 815 |
| Tyr Val Lys Asn Thr His Ala Thr Thr His Asn Ala Tyr Asp Leu Glu |     |     |
| 820   | 825 | 830 |
| Val Ile Asp Ile Phe Lys Ile Glu Arg Glu Gly Glu Cys Gln Arg Tyr |     |     |
| 835   | 840 | 845 |
| Lys Pro Phe Lys Gln Leu His Asn Arg Arg Leu Leu Trp His Gly Ser |     |     |
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| Pro Pro Glu Ala Pro Val Thr Gly Tyr Met Phe Gly Lys Gly Ile Tyr |     |     |
| 885   | 890 | 895 |
| Phe Ala Asp Met Val Ser Lys Ser Ala Asn Tyr Cys His Thr Ser Gln |     |     |
| 900   | 905 | 910 |
| Gly Asp Pro Ile Gly Leu Ile Leu Leu Gly Glu Val Ala Leu Gly Asn |     |     |
| 915   | 920 | 925 |
| Met Tyr Glu Leu Lys His Ala Ser His Ile Ser Lys Leu Pro Lys Gly |     |     |
| 930   | 935 | 940 |
| Lys His Ser Val Lys Gly Leu Gly Lys Thr Thr Pro Asp Pro Ser Ala |     |     |
| 945   | 950 | 955 |
| Asn Ile Ser Leu Asp Gly Val Asp Val Pro Leu Gly Thr Gly Ile Ser |     |     |
| 965   | 970 | 975 |
| Ser Gly Val Asn Asp Thr Ser Leu Leu Tyr Asn Glu Tyr Ile Val Tyr |     |     |
| 980   | 985 | 990 |
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Phe Lys Thr Ser Leu Trp

1010

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